UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,140	06/16/2005	Peter Bernstein	133087.02301(100945-1PUS)	9263

52286 7590 02/18/2009

Pepper Hamilton LLP
400 Berwyn Park
899 Cassatt Road
Berwyn, PA 19312-1183

EXAMINER	
O DELL, DAVID K	
ART UNIT	PAPER NUMBER
1625	
MAIL DATE	DELIVERY MODE
02/18/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,140	BERNSTEIN ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4-7 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 4-7, 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 2, 4-7, 20 are pending in the current application.

2. This application is a 371 of PCT/SE03/02004 filed 12/18/2003 which claims benefit of 60/435,130 filed 12/20/2002.

Claim Rejections/Objections Maintained/ New Grounds of Rejection

3. The rejection of claims 2, 4-7, 20 under 35 U.S.C. 103(a) as being obvious over Lowe et. al. WO 9805292, is maintained. Applicant's arguments filed November 18, 2008 have been fully considered but they are not persuasive. The applicant has argued that Stevenson does not motivate one to choose the compounds with the amino group linker, since compound 49 with the CH_2-NH-CH_2 group was less potent than the compound 12 with the CH_2-O-CH_2 group (12.6 ± 8.8 in the former IC_{50} vs. 0.95 ± 0.41 IC_{50} in the latter). The examiner submits that based on the experimental error involved these two values are ostensibly the same, or marginally better with the CH_2-O-CH_2 group (around 3 fold). Both of these linkers will work and a skilled artisan would use either one or even both. What should be taken away from the teaching of Stevenson are two key conclusions: 1) The nature and substitution pattern of the aryl moiety has the most profound effect on the activity (See Table 1). 2) The activity of compounds like 48 and 49 is governed by the identity of the aryl ring. The large difference in activity between compound 48 and 49 is quite remarkable (compound 48 is essentially dead, while 49 is very potent). This is exactly the place one would explore further SAR, in a place where big effects can be obtained. The fact that such changes gave these dramatic effects is a strong motivation to continue to modify this position and as Stevenson suggests these aryl group modifications are most preferably groups with electron withdrawing substituents. The substituent applicant has

modified the teaching of Stevenson with is the heavily optimized naphthyl group developed by Bernstein. This is not as the applicant's have suggested a hindsight reconstruction by the examiner, but rather a case of *prima facie* obviousness. If in fact Bernstein were working on a different receptor, a different biological target, this argument would be very persuasive, however the facts are that both Stevenson and Bernstein were working on very specific piperidine ligands for a single receptor, namely the NK1 receptor. One working in this field would have been immediately aware of the teaching of Bernstein and its relevance to the compounds of Stevenson. Stevenson experimented in a limited way with the aryl portion, but suggested that aryl groups bearing electron withdrawing groups would be preferred. Bernstein modified the phenyl portion by screening a diverse set of compounds where the phenyl was replaced with "over 100 aryl, heteroaryl and arylalkyl groups". In the words of Bernstein the result of this study was "the most potent, dual acting compound to come out of this array was the naphthamide **2a**".

The double patenting rejection of claims 2, 4-7, 20 is maintained because the two way test for ODP was met. While the teaching of Stevenson might suggest that such that the rejection would only meet a one-way test, the explanation of Stevenson used in the rejection was just a possible explanation: "The explanation for this may lie in the fact that in compounds such as 2 the benzylic amino group is directly attached to the piperidine/ quinuclidine ring.", and might lead one to a conclusion, however far more compelling is experimental data provided by Elliot. Elliot et. al. *Bioorganic & Medicinal Chemistry Letters* 12 (2002) 1755–1758, states that "A number of different linkers are tolerated, most notably the amides 2 and 15, the amine 17 and ether 23. The relatively poor affinity of the propyl linker 24 (hNK1 IC50 40nM) shows that a

heteroatom in the chain is beneficial." which very clearly allows the rejection to meet the two way test. While Stevenson suggests that the amides might be better than amines, he doesn't suggest that the amines don't work, in fact they work just fine. There is a finite group of linkers to choose from and all appear to give good results.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 2, 4-7, 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stevenson, Graeme I. et. al. "4,4-Disubstituted Piperidine High-Affinity NK1 Antagonists: Structure-Activity Relationships and in Vivo Activity" *Journal of Medicinal Chemistry*, **1998**, *41*, 4623-4635, cited on the IDS, in view of Bernstein et. al. *Bioorganic and Medicinal Chemistry Letters* **2001**, *11*, 2769-2773. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Determination of the scope and content of the prior art

(MPEP 2141.01)

Stevenson et. al. teaches compounds that are analogs of the compounds of the instant case that have the same utility. In particular the compounds on page 4630 Table 4:

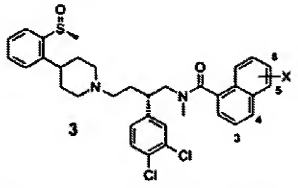
Table 4. Alternative Linkers

Compound	Ar	hNK1 IC_{50}[a]	Formula	Analysis
48		> 100[b]	$C_{28}H_{32}N_2O$	C, H, N
49		12.6 ± 8.8	$C_{21}H_{22}N_2F_6$	C, H, N
57		63 ± 7	$C_{28}H_{28}NF_6$	C, H, N[c]

[a] Displacement of [^{125}I]-labeled substance P from the cloned receptor expressed in CHO cells ($n = 3$). [b] 31% and 23% @ 0.1 μM. [c] $C_{28}H_{28}NF_6$ requires 415.1734, found 415.1750

In order to buttress the examiner's conclusion and show that the examiner is not taking official notice, the examiner submits that Bernstein et. al. "Discovery of Novel, Orally Active Dual NK1/NK2 Antagonists" *Bioorganic and Medicinal Chemistry Letters* **2001** *11*, 2769-2773, clearly teaches the exact modification (down to the very precise substituents on the naphthyl ring), thus the use of naphthyl in these NK1-antagonists and the substitution of naphthyl for phenyl was very well known even in this very small field. Starting with the known selective antagonist SR48968, Bernstein modified the phenyl portion by screening a diverse set of compounds where the phenyl was replaced with "over 100 aryl, heteroaryl and arylalkyl groups". In the words of Bernstein the result of this study was "the most potent, dual acting compound to come out of this array was the naphthamide **2a**". Bernstein goes on to describe that "to follow-up the discovery of this naphthamide we explored the effect of substituents on the naphthalene ring."

Table 2. Exploration of varying substituents in 3-X-naphthamides



3

Compd	3 X=	pK_B[a] NK_1	pK_B[a] NK_2	Dose ratio[b]	
				NK_1	NK_2
2a	H	7.89±0.08	8.18±0.28	52	262
3b	NO_2	8.16±0.10	9.03±0.18	50	321
3c	Br	8.15±0.34	7.67±0.24	43	34
3d (ZD6021)	C≡N	8.98±0.17	8.26±0.10	144	74
3e	SO_2CH_3	7.43±0.25	7.35±0.04	22	28
3f	Cl	7.15±0.12	7.10±0.09	13	31
3g	OMe	7.95±0.04	7.70±0.06	47	77
3h	CO_2H	5.68±0.14	6.86±0.11	ND[c]	ND
3i	CH_3	8.03±0.04	7.29±0.21	26	123
3j	CH_2CN	8.42±0.24	6.99±0.06	133	39
3k	Ac	7.41±0.35	7.17±0.13	41	156
3l	$C(=CH_2)CH_3$	7.24±0.19	7.24±0.29	31	75
3m	SO_2NH_2	7.54±0.04	7.02±0.21	170	7
3n	$CON(Me)_2$	5.17±0.22	7.31±0.33	ND	ND
3o	C≡CH	7.71±0.14	7.44±0.22	23	34
3p	F	7.90±0.07	8.15±0.23	12	52
3q	CF_3	7.84±0.07	6.45±0.25	ND	ND

It is interesting that 3-cyano-naphthyl was the preferred substituent, as in compound **4**. This 3-cyano naphthyl group is also the preferred substituent of the instant case and is what

distinguishes these compounds from those of Stevenson et. al. There can be no doubt that this was the preferred substituent.

Ascertainment of the difference between the prior art and the claims

It is clear that the prior art differs only in the presence of various phenyl groups for the heavily optimized naphthyl of Bernstein.

(MPEP 2141.02)

Stevenson et al. do not expressly teach the exact compounds of the instant case.

Finding of prima facie obviousness

Rational and Motivation
(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use analogs of those of Stevenson et. al. to produce the instant invention. Analogs differing only in the substitution of phenyl for naphthyl, are *prima facie* obvious, and require no secondary teaching when the utility is the same. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these compounds on the expectation that such close analogues would have similar properties and upon the routine nature of such experimentation in the art of medicinal chemistry. It would be routine for the chemist to replace phenyl with naphthyl especially since the chemistry developed by Stevenson was in place and the synthesis only involved using an appropriate naphthyl halide (see scheme 5 of Stevenson et. al.), moreover Stevenson suggests that lipophilicity of the aryl moiety

to be important since compound **49** bearing the lipophilic CF_3 group has increased potency over compound **48** (see table 4 above), thus naphthyl being slightly more lipophilic would have increased potency. Naphthyl and more specifically, the 3-cyano naphthyl group is also the preferred substituent of Bernstein et. al. who showed the preference for naphthyl over phenyl. There can be no doubt that this was the preferred substituent.

> *Ex parte WESTFAHL*, 136 USPQ 265 (Bd. Pat. App. & Int. 1962):
>
> "Appellant relies upon the case of In re Jones, 32 CCPA 1020, 1945 C.D. 304, 579 O.G. 148, 149 F.2d 501, 65 USPQ 480 , as supporting the patentability of claim 8 because in that case a naphthyl compound was held to be patentable over the corresponding phenyl compound. However, the rejection in that case was based upon the premise, held to be untenable by the court, that benzene and naphthalene are members of a homologous series. In the present case, **the examiner does not rely upon any theory of homology but has cited a reference (Richter II) teaching that naphthalene is very similar to benzene and forms a series of analogous derivatives**."

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

One of ordinary skill is also one of "ordinary creativity, not an automaton". See Leapfrog Enterprises Inc. v. Fisher-Price. and Mattel Inc. UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT "An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others

would not. See KSR Int'l Co. v. Teleflex Inc., 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at 12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 2, 4-7, 20 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of copending Application No. 10/525,303 in view of Stevenson et. al. "4,4-Disubstituted Piperidine High-Affinity NK1 Antagonists: Structure-Activity Relationships and in Vivo Activity" *Journal of Medicinal Chemistry*, **1998**, *41*, 4623-4635, cited on the IDS, in further view of Elliot et. al. Bioorganic & Medicinal Chemistry Letters 12 (2002) 1755–1758. This is a provisional obviousness-type double patenting rejection.

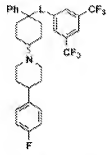
Copending Application No. 10/525,303 teaches compounds, compositions, and methods with compounds that are the amide analogs of the compounds of the instant case that have the same utility.

Ascertainment of the difference between the claims

It is clear that the copending application differs only in the presence of a carbonyl group for the methylene of the instant case. The interchangability of the linking moieties (amine vs. amide) is taught by Elliot et. al. in his NK-1 antagonists.

"Table 1 summarises the effect of modifications to the amide linker of 2. Throughout, trans-isomers have higher affinity than the corresponding cis-isomers. **A number of different linkers are tolerated, most notably the amides 2 and 15, the amine 17 and ether 23.** The relatively poor affinity of the propyl linker 24 (hNK_1 IC_{50} 40nM) shows that a heteroatom in the chain is beneficial. This could be because the heteroatom introduces a conformational bias which favours binding, or due to participation of the heteroatom in a hydrogen bond to the receptor." Pg. 1756-1757 Bioorganic & Medicinal Chemistry Letters 12 (2002) 1755–1758

Table 1. Linker replacements



Compd	-L-	Stereochemistry	hNK$_1$ IC$_{50}$ (nM)[a]
11		*cis*-	150 ± 80
2		*trans*-	0.34 ± 0.10
12		*cis*-	250 ± 26
13		*trans*-	6.3 ± 2.5
14		*cis*-	85 ± 46
15		*trans*-	0.70 ± 0.44
16		*cis*-	82 ± 0
17		*trans*-	1.7 ± 0.6
18		*cis*-	140 ± 49
19		*trans*-	2.5 ± 0.6
20		*cis*-	50% @ 1000
21		*trans*-	120 ± 99
22		*cis*-	59 ± 18
23		*trans*-	4.2 ± 1.9
24		1:1 *cis*- and *trans*-	40 ± 3

[a]Displacement of [^{125}I]-labelled substance P from the cloned receptor expressed in CHO cells. Data are mean ± SD ($n = 3$).[5]

They are all "tolerated" according to Elliot.

(MPEP 2141.02)

The copending application is not directed to the exact compounds of the instant case.

Finding of prima facie obviousness

Rational and Motivation

(MPEP 2142-2143)

It would have been obvious to one of ordinary that the amide analogs of the instant case would be active as taught by Elliot et. al. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these compounds on the expectation that such close analogues would have similar properties and upon the routine nature of such experimentation in the art of medicinal chemistry. It would be routine for the chemist to make the amides especially since the chemistry developed by Stevenson was in place and the synthesis only involved using an appropriate naphthyl halide or acid (see scheme 5 of Stevenson et. al.). Elliot et. al. teaches that they are in fact interchangeable.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims and those of the copending application is a clear case of double patenting.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625